NDA 50-420/S-070, S-071
NDA 50-627/S-006, S-007

APR 12 2000

Aventis Pharmaceuticals
Attention: Carol Childers, PharmD
Regulatory Analyst
10236 Marion Park Drive
P. 0. Box 9627
Kansas City, MO 64134-0627

Dear Dr. Childers:

Please refer to your supplemental new drug applications dated March 17, 1998 and November 19, 1999, received March 18, 1998 and November 23, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rifadin® (rifampin capsules) Capsules, 150 mg and 300 mg (NDA 50-420/S-070, S-071, respectively) and Rifadin® (rifampin for injection)
Injection, 600 mg (NDA 50-627/S-006, S-007, respectively).

We acknowledge receipt of your submissions to these NDAs dated February 1, 2000 and March 24, 2000, received February 2, 2000 and March 27, 2000.

These supplemental new drug applications provide for the following changes to the Rifadin® label:

1.PRECAUTIONS

The **Laboratory Tests** subsection was expanded and revised to read:

> "Adults treated for tuberculosis with rifampin should have baseline measurements of hepatic enzymes, bilirubin, serum creatinine, a complete blood count, and a platelet count (or estimate). Baseline tests are unnecessary in pediatric patients unless a complicating condition is known or clinically suspected.
> Patients should be seen at least monthly during therapy and should be specifically questioned concerning symptoms associated with adverse reactions. All patients with abnormalities should have follow-up, including laboratory testing, if necessary. Routine laboratory monitoring for toxicity in people with normal baseline measurements is generally not necessary."

- The **Drug Interactions** subsection, ENZYME INDUCTION subsection was revised to add claithromycin, quinine, and tricyclic antidepressants (e.g. amitriptyline, nortriptyline) to the second paragraph as follows:

> "Rifampin has been reported to accelerate the metabolism of the following drugs:
> anticonvulsants (eg, phenytoin), antiarrhythmics (eg, disopyramide, mexiletine, quinidine,

tocainide), oral anticoagulants, antifungals (eg, fluconazole, itraconazole, ketoconazole), barbiturates, beta-blockers, calcium channel blockers (eg, diltiazem, nifedipine, verapamil), chloramphenicol, clarithromycin, corticosteroids, cyclosporine, cardiac glycoside preparations, clofibrate, oral or other systemic hormonal contraceptives, dapsone, diazepam, doxycycline, fluoroquinolones (eg ciprofloxacin), haloperidol, oral hypoglycemic agents (sulfonylureas), levothyroxine, methadone, narcotic analgesics, nortriptyline, progestins, quinine, tacrolimus, theophylline, tricyclic antidepressants (eg, amitriptyline, nortriptyline), and zidovudine. It may be necessary to adjust the dosages of these drugs if they are given concurrently with rifampin."

- The **Drug Interactions** subsection, OTHER INTERACTIONS subsection was revised to add the following statements, which are now the first, and second paragraphs in this subsection:

"When the two drugs were taken concomitantly, decreased concentrations of atovaquone and increased concentrations of rifampin were observed.
Concurrent use of ketoconazole and rifampin has resulted in decreased serum concentrations of both drugs. Concurrent use of rifampin and enalapril has resulted in decreased concentrations of enalaprilat, the active metabolite of enalapril. Dosage adjustments should be made if indicated by the patient's clinical condition."

- The **Drug/Laboratory Interactions** subsection was expanded so that the first paragraph now reads:

"Cross-reactivity and false-positive urine screening tests for opiates have been reported in patients receiving rifampin when using the KIMS (Kinetic Interaction of Microparticles in Solution) method (eg, Abuscreen OnLine opiates assay; Roche Diagnostic Systems). Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish rifampin from opiates."

- A new **Geriatric Use** subsection was added to the end of this section to read:

"Clinical studies of Rifadin did not include sufficient numbers of subjects aged 65 and over to determine Whether they respond differently from younger subjects. Other
reported clinical experience has not identified differences in responses between the
elderly and younger patients. Caution should therefore be observed in using rifampin in elderly patients. (See **WARNINGS**.)"

2. ADVERSE REACTIONS

- "Psychosis has been rarely reported." has been added to the Central Nervous System subsection and is now the last sentence in this section.

3. OVERDOSAGE

- This section was revised and expanded to read:

<u>Signs and Symptoms</u>
Nausea, vomiting, abdominal pain, pruritus, headache, and increasing lethargy will probably occur within a short time after ingestion; unconsciousness may occur when there is severe hepatic disease. Transient increases in liver enzymes and/or bilirubin may occur.

Brownish-red or orange discoloration of the skin, urine, sweat, saliva, tears, and feces will occur, and its intensity is proportional to the amount ingested.
Facial or periorbital edema has also been reported in pediatric patients. Hypotension, sinus tachycardia, ventricular arrhythmias, seizures and cardiac arrest were reported in some fatal cases.
Acute Toxicity
The LD_{50} of rifampin is approximately 885 mg/kg in the mouse, 1720 mg/kg in the rat, and 2120 mg/kg in the rabbit.
The minimum acute lethal or toxic dose is not well established. However, nonfatal acute overdoses in adults have been reported with doses ranging from 9 to 12 gm rifampin. Fatal acute overdoses in adults have been reported with doses ranging from 14 to 60 gin. Alcoholor a history of alcohol abuse was involved in some of the fatal and nonfatal reports. Nonfatal overdoses in pediatric patients ages 1 to 4 years old of 100 mg/kg for one to two doses has been reported.
Treatment
Intensive support measures should be instituted and individual symptoms treated as they arise. Since nausea and vomiting are likely to be present, gastric lavage is probably preferable to induction of emesis. Following evacuation of the gastric contents, the instillation of activated charcoal slurry into the stomach may help absorb any remaining drug from the gastrointestinal tract. Antiemetic medication may be required to control severe nausea and vomiting. Active diuresis (with measured intake and output) will help promote excretion of the drug. Hemodialysis may be of value in some patients.

4. DOSAGE AND ADMINISTRATION

- "IV doses are the same as those for oral" was added and is now the second sentence in this section.

- The adult dosage was revised in the Tuberculosis subsection to read:

  "Adults: 10 mg/kg, in a single daily administration, not to exceed 600 mg/day, oral or IV"

- An Incompatibilities subsection was added following the **Preparation of Solution for IV Infusion** subsection to read:

  "Incompatibilities: Physical incompatibility (precipitate) was observed with undiluted (5 mg/mL) and diluted (1 mg/mL in normal saline) diltiazem hydrochloride and rifampin (6 mg/mi, in normal saline) during simulated Y-site administration."

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted March 24, 2000).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 50-420/S-070, S-071 and NDA 50-627/S-006, S-007." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and &copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Robin Anderson, Regulatory Review Officer, at (301) 827-2127.

Sincerely,

Renata Albrecht, M. D.
Acting Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research